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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07K 1/00 | A2

(11) International Publication Number: WO 00/15653

(43) International Publication Date: 23 March 2000 (23.03.00)

(21) International Application Number: PCT/GB99/03088

(22) International Filing Date: 16 September 1999 (16.09.99)

(30) Priority Data:
9820208.8 16 September 1998 (16.09.98) GB

(71) Applicant (*for all designated States except US*): CENTRAL RESEARCH LABORATORIES LIMITED [GB/GB]; Dawley Road, Hayes, Middlesex UB3 1HH (GB).

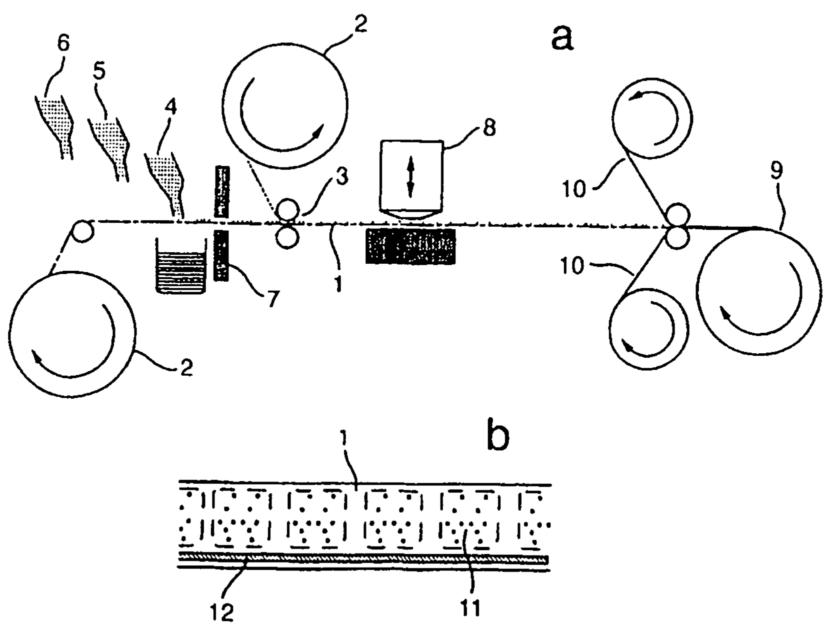
(72) Inventor; and
(75) Inventor/Applicant (*for US only*): SHAW, John, Edward, Andrew [GB/GB]; 45 Colne Avenue, West Drayton, Middlesex UB7 7AL (GB).

(74) Agent: WALKER, Neville, Daniel, Alan; QED I.P. Services Limited, Dawley Road, Hayes, Middlesex UB3 1HH (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*Without international search report and to be republished upon receipt of that report.*

(54) Title: APPARATUS FOR, AND METHOD OF, STORING A PLURALITY OF CHEMICAL COMPOUNDS




(57) Abstract

Combinatorial chemistry is a technique of generating large numbers of chemical compounds which are stored in libraries. The invention provides apparatus and method of storing the libraries on a variety of media, for rapid and easy access. An example of a storage medium is a tape wound on a reversible spool system. The tape has a unique address system and is able to store a very large number of chemical species in individual enclosed cells. Access to each cell may be by way of a syringe. This permits a small amount of each substrate to be removed without cross-contaminating another cell.

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# Apparatus for, and method of, storing a plurality of chemical compounds

This invention relates to an apparatus for, and method of, storing a plurality of chemical compounds. More particularly, but not exclusively, the invention is suitable for storing chemical compounds in, and retrieving chemical compounds from, for example, a combinatorial chemical library.

Combinatorial chemistry is a means of preparing large groups of different but related chemical species, often referred to as chemical libraries, generally by sequentially adding a range of component structures by reaction with precursors. Combinatorial chemical libraries consist of all or a subset of products from sequential combinations from a group of chemical compounds or building blocks. Typically the chemical compounds, also known as products, include 3 to 5 combined units where each of these units is from one or more sets of, typically 10 to 50, chemical compounds with sufficient similarity within each set to allow the addition of each chemical compound within a set to one or more prior formed units. Products may be formed by series of reactions carried out wholly in solution. However methods whereby products are built up while attached to a solid support material, particularly in bead form, are often favoured.

For example there may be a set of initial chemical building blocks, which may be bound to a carrier substrate material. These building blocks may be referred to as :

$$A1,\ A2,\ A3,\ .........An_A$$

and a second set of chemical building blocks:

$$B1,\ B2,\ B3,\ .........Bn_B$$

and a third set:

$$C1,\ C2,\ C3,\ \ldots\ldots\ldots Cn_C$$

where the chemical building block sets corresponding to *A*, *B*, and *C*, may be different or the same, and the numbers within each set (corresponding to $n_A$, $n_B$, and $n_C$) may be different or the same.

WO-A1-9812559 (Demers) describes a technique of carrying out combinatorial chemistry on a planar substrate in compact disc (CD) like format using laser to address and activate areas for reaction. An ink jet printer is used for delivering reagents.

Products to be formed may thus be characterised, for a three building block case, as all or a subset of combinations *ApBqCr* where *p*, *q*, *r* may be *1* to $n_A$, *1* to $n_B$, and *1* to $n_C$ using the representation indicated above. Four or five building block products may similarly be represented as *ApBqCrDs* or *ApBqCrDsEt*.

*A*, *B*, *C* etc in the products will be derivative of, rather than identical to, *A*, *B*, *C* in individual reagent sets, as particular bonds are formed and broken with elimination and addition of other moities as a result of reaction and binding of the chemical building blocks, and also resultant conformal changes possibly including ring formation or breaking.

WO-A1-9719958 (Mandecki) describes a technique of tagging beads for combinatorial chemistry.

In synthesis of compounds on beads by the so-called 'split synthesis' method, beads provide manipulable supports to which initial components may be bound and which may be exposed to a series of processes including reaction with selected reagents interspersed with washing, separation, and mixing operations. A diverse range and large number of products may conveniently be generated on a collection of beads. This may be performed so as to ensure that each bead bears only one of those final products.

Typically for 'split synthesis' there are added primary, secondary, tertiary, and possibly more series of building blocks (hereinafter indicated by italic capitals *A, B, C, D*) each of which series has diversity elements (hereinafter indicated by numbers or lower case letters *1* to $n_X$ added as postscripts to the capitals representing building block series). Any compound generated as a result of the split synthesis process may be identified as *ApBqCrDsEt* etc. The chemicals corresponding to *A, B, C, D* may be different or the same. The level of diversity $n_A$, $n_B$, $n_C$, $n_D$ etc corresponding to each series may be different or the same.

Typically the number of series of building blocks will be relatively small (e.g. 2 to 5 corresponding to *ApBq* to *ApBqCrDsEt*, while the number of diversity elements in each series may be relatively large ( e.g. $n$ =10 to 50). For repeat or supplementary syntheses, as after initial testing of libraries, or on the basis of modelling or previously known activity, the numbers of diversity elements for each synthesis stage may be quite limited.

WO-A1-973598 (Ontogen) describes a technique of combinatorial chemistry performed on solid supports. Synthesis occurs on a series of solid supports in an array format. Changes in orientation of the array with respect to a fluid reagent delivery manifold, allow a number of combinations to be achieved. Also disclosed is a distribution of solid supports in a number of arrays, carrying out a stage of reaction with different reactants on each array, and redistributing supports in another set of arrays and then carrying out one or more further stages of reaction with different reactants on each of a new set of arrays.

A disadvantage of the simple application: the basic 'split synthesis' method, is that information on the sequence of reactions carried out on any individual bead, and hence the product it bears, is not recorded except in the identity of the bound product. The range of species *ApBqCr* etc may be formed but whether in solution or on beads mixing results in loss of information on identity, and individual products can only be identified by subsequent analysis. Analytical processes to determine the identity of products can be very time consuming, difficult and expensive and to some extent negate the usefulness of the 'split synthesis' method in producing large chemical libraries.

It is particularly desirable that the location as well as the identity of each product species can be easily and rapidly identified. It is also desirable that the methods used be adaptable to allow production of subsets of the products of interest to be readily produced by the same procedures, and to allow production of larger quantities of materials within limited subsets.

A number of ways have been suggested for 'tagging' beads to allow the reaction sequence for each to be recorded, but these can either introduce problems with the chemistry or involve slow 'read' processes as in the use of chemical markers such as a range of halogenated hydrocarbons absorbable by beads and readable by gas chromatography, or involve difficulties in the handling, marking and reading of the small soft near spherical particles. Typically particles are less than 1 x $10^{-3}$ m in diameter.

WO-A1-9624061 (Ontogen) describes how pieces of solid support and are tagged using recordable tags. However, the method is complex and expensive.

At its extreme, spatial segregation can correspond to carrying out separately the reaction sequences on individual reagent groups to generate individual products in separate containers. This however can result in a great increase in operational complexity, time requirements, and cost compared with the standard split synthesis procedures.

An object of the present invention is to maintain the spatial segregation and information content of the split syntheses procedure. Another is to overcome the aforementioned problems.

1. According to the present invention there is provided apparatus for storing a plurality of chemical compounds comprising:

i) a support substrate on which is defined a plurality of enclosures each being capable of receiving a chemical compound for storage;

ii) said substrate having defined thereon a plurality of regions each having a unique address associated therewith;

iii) means for presenting a particular enclosure, in accordance with a selected address, characterised in that the enclosures are sealed one from another, so as to prevent cross-contamination of chemical compounds.

Thus the present invention and related methods for carrying out combinatorial chemistry and product testing, retain identity information using substrate which may be assessed, for example by a syringe, so as to access the chemical compound in the enclosure, remove a portion and enable the remaining chemical compound to exist intact in the enclosure.

The substrate may be supported on an elongate substrate, such as for example, a tape.

Preferably there is provided means for relating an amount of displacement in dependence upon the address of a region. For example, a location of a chemical compound or product may be related to its position along said tape.

Preferably the substrate includes a solid support material in the form of particles of similar size or smaller than conventionally used for beads, supported on or between sheets of porous, chemically inert material, such as for example, non woven polypropylene, glass fibre, synthetic plastics material or cellulose paper. Said at least one sheet forming material is receptive to indelible marking, through e.g. printing, laser marking, magnetic labelling or mechanical deformation, such as punching.

Reactions may also be performed in an enclosure by delivery of a chemical. The process of carrying out reactions on areas of substrate includes transferring reagents and solutions to and from the substrate or tape by a variety of means including printing technologies, exposure to fluid streams, transfer of tape through vessels containing reactants and fluids, and transfer of material between tapes or tapes and sheets by bringing them into contact for wash through, blotting, or transfer printing processes.

The tape or other substrates are then encapsulated so as to permit, for example, access by a syringe, and prevent egression when the syringe is removed.

According to another aspect of the invention there is provided a method of storing a plurality of chemical compounds for retrieval comprising the steps of:

i) disposing a chemical compound on a region of a substrate;

ii) retaining said chemical compound so that it is isolated from other compounds on the substrate, and accessible from a location external to the enclosure;

iii) arranging an address to be associated with said region; and

iv) repeating steps i) to iii) on different regions of said substrate.

One or more processing steps may be performed on selected compounds on regions of the substrate. The processing steps may include chemical reactions with other chemicals or compounds so as to create products. The substrate or tape may be transparent to a particular band of radiation which passes there through and which may be used to ascertain the extent of a reaction or contents of an enclosure. Such a beam of radiation for example may be used in spectral analysis.

Preferably products created may be retained on the substrate or formed on or transferred to a further substrate. Transfer may be by way of a syringe.

According to a further aspect of the invention there is provided a method of retrieving a chemical compound from a plurality of stored compounds on a substrate from address information, comprising the steps of:

i) determining from said address information a position of the compound. stored in an enclosure, on the substrate; and

ii) displacing the substrate so that said region, supporting the compound, is presented for retrieval; characterised in that means is provided for accessing an enclosure

to remove a portion of the chemical compound, the enclosure re-sealing in order to maintain the remaining chemical compound in the enclosure intact.

The term "retrieval", for the purpose of this specification, includes analysis, removal, examination and/or testing.

One preferred technique allowing ordered handling and reaction of materials, while retaining information, is to employ some spatial segregation of reagents and products which can be maintained and monitored throughout a reaction sequence. This allows the final products to be identified by their positions within some field, and facilitates the marking of substrate areas with machine readable codes containing (or referencing) non-identity and history information. Such monitored spatial segregation may also be used to control test operations on the products for determining, for example, biological or pharmaceutical activity. Thus it is proposed that testing of products may be carried out using the same or similar apparatus as is used to produce libraries.

Procedures described below as 'Cut and Stack' and 'Tape Based' combinatorial chemistry are designed rapidly to bring together individual reagents in desired combinations and conveniently control and allow recording of the sequence of operations. Preferably this is achieved by providing physical means for displacing and ordering products and chemical intermediates bound to solid substrates. Means may be provided for recording the sequence of operations forming a product and associating it to its position.

Means for marking areas of the solid substrate or carrier sheet, film, or tape with a mechanically readable record may be provided. In existing 'cut and stack' combinatorial chemistry procedures products are built on sheet material which may be sub-divided into separable smaller sections or tabs which can be conveniently handled, ordered and monitored by equipment related to that used for reading cards. Libraries of products may be built on extended tapes which may be manipulated on tape winding, recording, and reading equipment.

Further possible advantages beyond the information retention may be gained from the use of planar porous media retaining the solid phase substrate materials on which the products and intermediate chemistries are bound. The conventional solid substrate beads are relatively soft, especially when swollen by solvent, and retention within an inert web material prevents mechanical damage, and reduces problems with beads sticking together. This allows greater freedom in choice of reacting conditions, solvents, and concentrations. Further the transfer of material within the beads during reaction, washing, or elutration will involve diffusive processes. This can introduce time delays which increase in proportion to the square of the diffusing distance, which may be bead radius. Handling very much smaller free beads may cause problems, but inclusion of particles within a porous web can overcome the handling difficulties. Further retention of the product and intermediate chemical species, by for example, binding solid phase substrate materials within a porous web material, allows use of a filter stack geometry for exposure to solutions, and washing operations. This provides tight control over times for each operation and avoids extended settling and decantation operations.

It is possible that for both cut and stack, and tape based systems that in addition to the reagents being supplied in solutions that they may also be transferred to reaction zones on carrier sheets, films, or substrates. Further it is possible that the two systems may be used together with tapes being cut to form tabs, and tabs being spliced to form tapes.

Although the cut and stack, and tape based systems are described primarily in terms of generation of products in a spatially defined way, the advantages may be extended to product testing. Test chemistries or biological systems may also be applied in a planar array format, possibly absorbed on similar sheet materials. This allows product sheets and tests to be in contact, subjected to conditions allowing scope for interaction, e.g. addition of eluting chemistry for one material followed by diffusive transfer to the other. Where test results generate some optically monitorable change this may be read directly from the planar materials and correlated directly with the identity of product and test materials known to be present at those sites. The avoids problems with conventional beads of ordering and handling them to go into test procedures, and the identification of products on particular beads.

Embodiments of the invention will now be described, with reference to the Figures, in which:

Figures 1 to 3 show diagrammatical representations of cut and stack combinatorial chemical synthesis steps to form a library; and

Figures 4a to 13 show diagrammatically embodiments of the invention.

It is necessary to consider the numbers of products which may be generated in a combinatorial chemistry library and the resultant quantity of support media required whether in the form of numbers of beads or areas for any planar support.

The number of non-identical products which may be generated may be found by multiplying together the number of diversity elements from each stage of the synthesis operation. Thus for the example of a three stage synthesis with 30 *A*, 20 *B*, and 15 *C* elements the products of the form *ApBqCr* include all for $p=1$ to 30, $q = 1$ to 20, and $r = 1$ to 15. The total number of non-identical products will be 30 x 20 x 15 = 9000. This includes only the products formed by desired series of reactions and which can by the conventional split synthesis scheme, be formed so that no more than one is on any bead. Where for example chiral products may be formed and synthesis steps which are not chirally selective are used, the material formed on any bead or other portion of solid substrate may consist of, not a single product, but a mixture of optically active isomers. This aspect of the chemicals may be used in conjunction with a source of optical radiation to determine the state or plane of a chemical reaction.

An indication of the range of product numbers that may therefore need to be dealt with can be simply obtained for 2, 3, 4, or 5 stage syntheses taking a suitable number for the diversity at each stage. This is indicated in tables below, where columns show the numbers for equal diversity level at each stage.

The very large numbers at the bottom and right hand of each column correspond to extreme cases where numbers of products may tend to be unwieldy whatever the format for carrying out chemistry and test, but it desirable that methods be able to approach

those numbers. The standard bead materials with individual bead volumes of ~ $10^{-10}$ to $10^{-9}$ $m^3$ provide at least a method of generating the large product numbers in a reasonable volume. One cubic metre of beads is theoretically at least sufficient, even for the most extreme cases referred to in Table 1. Testing and identification however is more difficult than forming the larger numbers of products.

Forming, handling, and retaining products and identification information on planar media requires some material area per product. It seems reasonable to consider that might be as low as 1 mm square, but might need to be as high as 1 cm square. Areas per product of ~ 1 $cm^2$ will generally be sufficient for initial screening tests on chemical libraries. Greater areas may be desirable for products required for extensive testing but these may be generated by heat synthesis of individual products or of subsets of libraries.

Using product numbers from the ranges indicated in Table 2 and values of required area per product the total areas of planar substrates that need to be handled in cut and stack operations or as tapes may be computed. The results of such calculations are given in Table 2 below.

Examination of numbers and areas indicates that generally the quantities of sheet materials to be handed are not unreasonably large, especially for the more moderate library sizes (say 30 x 30 x 30 = 27000 products requiring 2.7 $m^2$ of sheet at 1sq. cm per product). Several sheets may be used to support a product library, and their number and size may be selected as convenience of handling dictates.

If a planar support medium is used it may be in tape form. The length of tapes and size of reels required can be calculated from areas and values for tape width and thickness. Typically web used to carry bound chemicals is significantly thicker than magnetic recording tape but overall dimension may not be very much greater than those for photographic film stock. Thickness' should generally be less than (or no greater than) the diameter of beads used for combinatorial chemistry and may be ~ 0.1 to 0.5 mm. Tape widths may conveniently be 1 to 10 cm. For illustrative purposes Table 3 shows tape lengths and reel diameter calculated on the basis of tapes 0.2 mm thick and 10 mm wide, and 0.5 mm thick and 10 cm wide, each wound on 3 cm diameter spindles.

Examining Table 3 it is apparent that while whole libraries of up to about 100000 products may be accommodated on single tapes at a density of 1 product per $cm^2$, the reel sizes would become excessive for larger numbers of products. It will however generally be more convenient to produce libraries as groups of tapes. For example each of the first series of building block chemistries (*As*) may be attached to a different tape, each of which may be treated by procedures described below, in order to form a subset of the combinatorial library. As an example Table 4 below, contains values based on dividing combinatorial library across 20 tapes which corresponds to 20 diversity elements in the first series of chemical building blocks. The size of product libraries that can reasonably be accommodated scales simply with the number of tapes and that number may reasonably freely be selected to be large enough to facilitate handling of the chemical library.

Referring now to Figure 1 there is now described a procedure based on performing processes using a solid support formed or bound within a sheet of material.

Sheets of material 10 suitable for binding chemistries, or containing material and which are sufficiently porous to allow solutions to pass therethrough are wound onto rollers or supports 12. The sheets 10 optionally have identification printed or otherwise marked thereon. Small tags embedded at same time as small porous spheres or sheets (not shown).

As indicated in Figure 1, at a first synthesis step separate sheets attach a chemical from a first group (*A*s). A number of diversity elements of series *A* chemistries are thus formed and bound on a series of sheets such that the solid support within or comprising each sheet is covered by one diversity element *Ap* and each of the chemistries is applied to at least one sheet. At least $n_A$ sheets, each corresponding to one of the diversity elements for series *A* are thereby formed. Each sheet may be marked by means of printing, laser marking, punching, or held in marked container, frame or folder.

Following the first synthesis step and prior to a second synthesis step, series *B* chemistries are added. At least one sheet of each of the chemistries *Ap* is cut into at least

$n_B$ strips, rectangles, or other conveniently shaped sub-divisions hereafter referred to as tabs 18. Tabs 18 from all types of series *A* sheets are brought together to form $n_B$ groups each containing all the series *A* diversity elements. This sorting and grouping may be carried out by automated equipment. These groups of tabs are taken through the chemical process steps to add series *B* building blocks with each of one the groups being processed with different reagent selection each corresponding to the the $n_B$ diversity elements of series *B*. Thus each tab contains only a single compound *ApBq* and every compound *ApBq* is formed on at least one tab.

The individual tabs 18 may be marked for identification by any means indicated above, and/or information on tab history and content retained by ordering the groups of tabs in some physical arrangement which is recorded and maintained throughout any synthesis stage. Such ordered physical arrangements of tabs may be achieved by means which include stacking, or physically linking to form strips or sheets, or inserting in a retaining framework or series of chambers.

Following the second synthesis step, and prior to a third synthesis step adding series *C* chemistries, at least one tab, bearing of each of the chemistries *ApBq*, is cut into $n_C$ smaller tabs, or other convenient subdivisions forming further tabs. The tabs are then grouped and processed in a manner analogous to that described above for series *B* chemistries so that each tab contains only a single compound *ApBqCr* and each compound *ApBqCr* is formed on at least one tab.

A similar process may be carried out for fourth or even fifth synthesis steps.

As described above the sheets are cut into sections between each synthesis stage, but it is also possible to perform cutting, marking, grouping, and stacking of planar sheet sections or tabs before carrying out the chemical reactions, and merely regrouping. and/or stacking between the synthesis stages. Whichever option is selected, the sheets or tabs may conveniently be ordered, grouped, and stacked by systems related to conventional automated card or tape handling equipment, possibly in combination with marking and reading units. The information on location and route of individual sections or tabs through the synthesis stages can be automatically recorded and held in a database, most

conveniently on a computer. The cutting, marking, dividing, grouping, and stacking operations may be controlled and modified throughout the original synthesis operations and in subsequent partial or complete repetitions of the synthesis operations. This may most conveniently be achieved by use of automated units linked into a computerised system.

Treatment of sheets or groups of tabs may be carried out by immersing in an excess of reaction medium, or by holding stacks in an apparatus allowing fluid to percolate or be driven through the stack by gravity or applied pressure difference. Some alternative embodiments are shown in Figure 2. The filter stack arrangement preferably has advantages in control of exposure time and reduced fluid volume requirements compared with similar systems.

Tape based combinatorial chemistry utilises a planar substrate material, but in the form of extended tapes which may be handled on reel to reel winding equipment. The tapes may be composed of solid substrate materials similar to those used for beads, but more generally they will consist of porous materials, such as webbing, enclosing particles of solid substrate materials on which products and intermediates may be bound. A variety of different means may be used to apply chemistries to a tape.

One such technique is indicated in Figure 3. This involves treating each of a series of tape lengths with a different diversity element of the first building block series. Thus if there are *p* type *A* chemistries then at least p tape length are treated to generate at least one tape bearing each of the chemistries *A1* to *Ap*. The tapes may also bear a readable, or write and read code so that the chemical exposure history may be recorded either on the tape or in some separate database which can be correlated with the code.

By employing cut and splice means tapes bearing a single chemical compound are converted to generate a number of new tapes with all or a selected subset of the first series compounds. Thus where *p* type *A* chemistries are to be used, each tape generated will have sections bearing each of the chemistries *A1* to *Ap* spliced together. The identity of material bound along the tape may be identified either by some code written onto the tape, or simply by the position along the length of the tape. The number of such tapes

generated will be at least equal to the number of second series diversity elements that are required i.e. at least $q$ tapes if $q$ type $B$ compounds are to be used. Applying the series of $q$ $B$ type chemistries, one each to the tapes will generate all the products $A1B1$ to $ApBq$ at known or readable positions along the tapes.

Again employing cut and splice means and equipment, the tapes for the second chemical addition stage are converted to generate a number of new tapes bearing each of the chemical compounds $A1B1$ to $ApBq$. The identity of material bound along the tape may be identified either by some code written onto the tape, or simply by the position along the length of the tape. The number of such tapes generated will be at least equal to the number of third series diversity elements that are required i.e. at least $r$ tapes if $r$ type $C$ chemistries are to be used. Applying the series of $r$ $C$ type chemistries, one each to the tapes will generate all the products $A1B1C1$ to $ApBqCr$ at known or readable positions along the tapes.

This procedure may in principle be continued for fourth or even fifth chemical building block additions within the limitations of useful slice section size.

Reel to reel media manipulation in combination with a range of means of applying chemical treatments provides a plurality of methods for creating chemical libraries and carrying out product testing on tape formats without, or at least with reduced, recourse to cut and splice operations. This may have advantages in terms of speed of operation and robustness. Operations, which it is proposed, may be used to build up and test chemical libraries on tape are described below with reference to Figures 4 to 13. Tape produced by these methods may also be used for cutting and splicing, or cutting and stacking. The equipment used for transferring, holding, and processing tape for combinatorial chemistry may include elements similar to that used for tape printing, and film processing, but may be more complex to allow joining of sections of web, sealing between layers and/or holding the tape in relatively static positions for reaction times (possibly in wound form). The tape may be substantially longeveous in cross-section, as is conventional magnetic recording tape, or the tape may have a series of sprocket holes incorporated into the structure as is conventional with photographic foil reels.

Conventional magnetic or optical recording media may be incorporated into or onto the tape web used as or to support the solid substrate for binding chemical compounds.

Application of reagents to form sets of chemical building blocks onto tapes may be achieved by a variety of methods for tapes formed by such steps as:

a) forming the tape web at least partly from a solid substrate media suitable for generating bound chemistries such those materials used for beads employed conventionally in combinatorial chemistry.

b) attaching solid substrate media such as beads or portions of sheet or tape form to a backing tape or web to provide strength and stability for handling.

c) enclosing solid substrate media such as beads or portions of sheet or tape form between tapes or webs to provide strength and stability for handling.

Solid substrate media to be incorporated in tape may be:

a) in untreated form, or

b) been first treated to attach binding reagents to allow bonding to chemical building blocks, or

c) been further treated to attach chemical building blocks, especially of the first series (*A1* to *Ap*).

An example procedure for the formation of a tape bearing a collection of solid substrate particles is represented in Figure 4a. The tape (11) containing particles is formed from by bringing together tapes or webs preferably of porous material from source reels or holders (12) by means of guides or rollers (13). Particles of solid substrate are fed from a reservoir such as a hopper onto one of the source webs before the two webs are brought together. Where particles bearing different building block chemistries are required on the tape, a series of reservoirs (14, 15, 16) may be selected. Following addition of particles to

the tape, information relating to particle type and history may be recorded on the tape by some writing mechanism (17). This may be a magnetic recording head if the tape bears suitable media, or may be a mechanism generating optically readable features such as a contact or ink jet printer, or a laser. The tape may pass through a mechanism (28) such as a press tool to produce a bond between webs forming the tape so as to enclose groups of particles. The tape is passed to a collection reel or holder (19). Sealing tapes (10) to enclose the web of the particle bearing tape may be applied before the tape is passed to the collection reel or holder. Such sealing tapes may be required where it becomes necessary to prevent transfer of material between sections of tape which may be in contact in the collection reel or holder (9).

Figure 4b shows the form which a section if tape (1) formed by the above procedure with enclosed groups of particles (11), and a strip of recoding media (12).

Where sets of solid substrate media bearing chemical building blocks are preformed the sets may be incorporated into individual tapes or selected sections of tapes as shown in Figures 4a and 4b retaining and recording information on which tapes or tape sections bear which chemistries. The information on location of each diversity item or building block may be recorded on the tape which may bear a recording media, or separately by any conventional means as a tape name or number, and where appropriate as a position along the tape such as distance from and end or mark, and where appropriate as distance across a tape width. Different diversity items or building blocks may be incorporated in the same length of tape but separated across the tape width being formed as strips or tracks parallel to the long axis of the tape. Such strips or tracks may also be incorporated to run diagonally across the tape.

Treatment of tapes to carry out chemical reactions, bind chemical building blocks or diversity items, and carry out test operations will now be described with reference to Figures 5 to 13.

Treatment of tape may be achieved by passing through containers of reagent solution. In Figure 5 tape (1) from a source reel (2) or other holder is passed along a systems of guides (3) such as rollers so that the tape can be passed through a series of vessels (13,

14, 15, 16, 17) before being passed to a collection reel (9) or other holder. Tape from the source reel may be passed through one or more vessels for washing, activating binding chemistry (13), adding building block chemistries (14), fixing building block chemistries and/ or washing off excess reagents and unwanted reaction products (15). Where more than one diversity element is to be incorporated on different sections of a single tape, means may be provided to change one or more of the vessels (14, 16, 17), or their contents, or move the tape guides to direct the tape through different vessels. A magnetic recording head (7) or other means may be provided for recording location and identity of diversity items or building blocks on the tape. Seals such as impervious tapes (10) may be used to enclose the web of the chemistry bearing tape may be applied before the tape is passed to a collection reel or holder. Such sealing tapes may be required where it becomes necessary to prevent transfer of material between sections of tape which may be in contact in the collection reel or holder (9).

Additionally a portion of the tape may be transparent so that an enclosure, containing a chemical compound, can be placed in a beam of optical radiation and the contents of the enclosure observed or analysed.

The chemical treatment of the tape may be achieved by immersing lengths of tape in reactant fluids and in activating, fixing, and washing solutions as shown in Figure 5, but may also be accomplished by passing fluid streams over or through the tape, by spraying fluids onto the tape, by printing reactants onto the tape by contact printing means or ink jet printing etc as indicated in Figures 6 to 13. Processing of tape and chemical building block addition and testing may be carried out with tape mechanisms allowing control of the speed and the direction of tape travel. By controlling tape position and application of chemistries, a selected group of products from a combinatorial chemistry library may be built up along tapes. Providing data recording and reading means on the tape, by bonding to magnetic recording tape, allows the identity of products on tape sections to be conveniently recorded and retrieved. The information may also be recorded simply on the basis of position on the tape. The information may conveniently be stored by computer and may also be employed in conjunction with computer control of tape drives and automated chemical treatment equipment.

Figure 6 shows transfer of tape (1) between holding reels (9 and 18). Source tapes for such an arrangement may be produced as indicated in Figures 4 and 5. Sealing tapes (10) may be applied to allow containment of materials on tapes in enclosures, while in holding reels and removed, possibly reversibly, to allow further chemical treatments or access, for example with a syringe; or analysis.

Application of chemical treatments and washing processes is by immersion of lengths of tape with washing, activation, and fixing at locations indicated by fluid containing vessels (20,21), and addition of building block chemistries at a location occupied by a reagent containing vessel (22). Diversity elements may be introduced by changing the content of the reagent containing vessel (22), or by substituting alternative vessels (23,24,25). Read/ write mechanisms (7, 9) may be included.

Figure 7 shows a similar arrangement to that in figure 6, but with washing, activation, fixing operations achieved by application of fluid streams or sprays onto the tape by appropriate mechanisms (26, 27). Tapes may be sealed after these processes have occurred. Reagents to add building block chemistries may similarly be applied by a selection of fluid sources (28, 29, 30).

As shown in Figure 8 the chemistries may also be applied by a print transfer mechanism (31) from reservoirs (32, 33, 34).

As shown in Figure 9 chemistries may also be applied by a coated roller transfer mechanism (35) from reservoirs (36, 37, 38).

As shown in Figure 10 the chemistries may also be applied by a non-contact ink jet print mechanism (39) from reservoirs (40, 41, 42, 43).

The treatments represented in figures 6 to 10 may be for adding building block chemistries to form combinatorial chemistry library species on tapes. The procedures may be simply adapted for application of test chemistries, including biological and biochemical tests, to the tapes. This provides a convenient means for evaluation of combinatorial chemistry libraries held in tape form. Monitoring equipment such as

optical detectors and associated optical components may conveniently be added to the systems. Results may be correlated with product identity and origin data obtained from attached recording media or from position on the tape and any associated data base or computer record.

A further class of alternatives may employ transfer of chemistries or material from one tape to another. Figure 11 shows this achieved by positioning adjacent to each other sections of tapes (44,45), and employing as stream of fluid (46) to transfer. The fluid may be chosen to elute material from one of the tapes and carry it into the other.

Figure 12 shows an alternative method of transferring material between adjacent sections of tapes (47,48) using a contacting print mechanism (49)

Figure 13 shows three views (Figures 13a, 13b, 13c) of an arrangement whereby sections of several tapes can be brought into close proximity to allow material transfer between tapes by means such as those indicated in Figures 11 and 12.

Combinations of the procedures and mechanisms indicated in Figures 5 to 13 may be used in combination to build up and test whole or partial combinatorial chemistry libraries based on tape. The tapes may additionally be employed in cut and splice and cut and stack arrangements described above.

1) A sufficient set of strips of each of the forms *ApBq* is formed that it is possible to process only a small fraction thereof to form the compounds *ApBqCr* as required for subsequent screening. In this way there is a significant stock of material of each of the forms *ApBq* which may be readily and rapidly converted in its entirety to a single given species of the form *ApBqCr* when the screening process indicated a need for a larger quantity of a specific material. (Or any of the various ways of only cutting tabs from part of the strips is used to ensure an excess of *ApBq* material.)

2) Each of the initial starting sheets is printed (or otherwise indelibly marked, such as laser marked) with a unique reference number in each of the areas which may subsequently be excised in the form of a strip or tab, thereby allowing rapid identification

and tracking through chemical processing of any given strip or tab and subsequent identification of the chemistry.

Here one should consider one "business model" of a company selling combinatorial chemical libraries. It may be desirable to sell a library of compounds which are labelled such that the vendor may readily identify the chemistry from the label, but the user can only so do by reference to the vendor.

3) Means may be provided to rejoin strips which have been cut to re-assemble sheets, where for example a strip of each of the chemistries *A1* to *Ap* is joined to form a sheet to which is added a specific chemistry *Bq*. By cutting such a sheet orthogonal to the original cut, strips containing each chemistry of the from the series *A1Bq* to *ApBq* (where the lower-case symbol represents a single defined chemistry) may be formed. Clearly the joining together of a set of strips of the above form with every chemistry *B1* to *Bq* being represented can result in sheets containing each chemistry of the series *A1B1* to *ApBq*. Adding a specific chemical building block *Cr* to such sheets results in sheets bearing each of the chemistries of the series *A1B1Cr* to *ApBqCr*. Such sheet forms may be convenient for high throughput screening of a full library rather than of a selected, representative level of diversity. The results obtainable by cutting and joining of strips to form sheets may similarly be achieved by arrangement where cut sections are combined into stacks where information is retained by the order within stacks, or by arrangements where sections are spliced into tapes and information is retained by position within tapes.

4) Procedures above have all been described in terms of forming single products only on a defined or separable portion of solid support medium whether it be in form of a bead, specific area on sheet or tab, or specific area on a tape. There may be advantage in modifying the procedures to produce subsets of a combinatorial library on each defined portion of solid support. Less support material in terms of numbers of beads, or areas of sheet or tape may be required, and the product may be particularly suitable for pooled testing. With conventional untagged beads could introduces further difficulties with identifying active products, but with tagged or effectively labelled support as may be provided by sheet or tape formats the problems could be limited. If the subsets on different tagged or labelled solid support portions are produced with overlap of content it

may be possible to identify active materials by deconvolution of test results on a group of solid support portions.

Table 1 - Product Numbers Generated in Combinatorial Chemistry

| Stages \ Diversity | 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|
| 1 | 10 | 20 | 30 | 40 | 50 |
| 2 | 100 | 400 | 900 | 1600 | 2500 |
| 3 | 1000 | 8000 | 27000 | 64000 | 125000 |
| 4 | 10000 | 160000 | 810000 | 2560000 | 6250000 |
| 5 | 100000 | 3200000 | 24300000 | 102400000 | 312500000 |

Table 2 - Planar Media Area ($m^2$) required for Product Numbers Generated in Combinatorial Chemistry

| | Area per Product - mm square | | | | |
|---|---|---|---|---|---|
| | 1 | 3 | 10 | 30 | 100 |
| Product Numbers | Total Plane Area - square metre | | | | |
| 1,000 | 0.001 | 0.003 | 0.01 | 0.03 | 0.1 |
| 10,000 | 0.01 | 0.03 | 0.1 | 0.3 | 1.0 |
| 100,000 | 0.1 | 0.3 | 1.0 | 3.0 | 10 |
| 1,000,000 | 1.0 | 3.0 | 10 | 30 | 100 |
| 10,000,000 | 10 | 30 | 100 | 300 | 1000 |
| 100,000,000 | 100 | 300 | 1000 | 3000 | 10000 |

Table 3- Tape Lengths and Reel Diameters for Full Library on Single Tape.

| | Tape thickness/ width | | | |
|---|---|---|---|---|
| | 0.2/ 10 mm | 0.2/ 10 mm | 0.5/ 100 mm | 0.5/ 100 mm |
| Product Numbers on single Tape | Length m | Reel diameter cm | Length m | Reel diameter cm |
| 1,000 | 10 | 6 | 1 | 4 |
| 10,000 | 100 | 16 | 10 | 9 |
| 100,000 | 1000 | 51 | 100 | 26 |
| 1,000,000 | 10000 | 160 | 1000 | 80 |
| 10,000,000 | 100000 | 505 | 10000 | 253 |
| 100,000,000 | 1000000 | 1600 | 100000 | 800 |

Table 4 - Tape Lengths and Reel Diameters for Full Library on 20 Tapes.

| | Tape thickness/ width | | | |
|---|---|---|---|---|
| | 0.2/ 10 mm | 0.2/ 10 mm | 0.5/ 100 mm | 0.5/ 100 mm |
| Product Numbers on 20 Tapes | Length m | Reel diameter cm | Length m | Reel diameter cm |
| 1,000 | 0.5 | 4 | 0.05 | 3.1 |
| 10,000 | 5 | 5 | 0.5 | 3.5 |
| 100,000 | 50 | 12 | 5 | 6.4 |
| 1,000,000 | 500 | 36 | 50 | 18.1 |

| | | | | |
|---|---|---|---|---|
| 10,000,000 | 5000 | 113 | 500 | 57.0 |
| 100,000,000 | 50000 | 357 | 5000 | 179.0 |

The invention has been described by way of examples only and variation may be made to the examples described without departing from the scope of the invention.

## CLAIMS

1. Apparatus for storing a plurality of chemical compounds comprising:

i) a support substrate on which is defined a plurality of enclosures each being capable of receiving a chemical compound for storage;

ii) said substrate having defined thereon a plurality of regions each having a unique address associated therewith;

iii) means for presenting a particular enclosure, in accordance with a selected address, characterised in that the enclosures are sealed one from another, so as to prevent cross-contamination of chemical compounds.

2. Apparatus according to claim 1 wherein the substrate includes a solid support material supported on or between sheets of porous, chemically inert material.

3. Apparatus according to claim 2 wherein the substrate includes materials from the set of: non-woven polypropylene, glass fibre, synthetic plastics material and cellulose paper.

4. Apparatus according to any preceding claim wherein means is provided for marking an address on the substrate.

5. Apparatus according to claim 4 wherein the means for marking is taken from the set of: a printer, a laser marker, a magnetic labeller and a mechanical deformer.

6. Apparatus according to any preceding claim wherein the substrate is supported on an elongate support, such as for example, a tape.

7. Apparatus according to any preceding claim wherein means is provided for relating an amount of displacement in dependence upon the address of a region.

8. Apparatus according to any preceding claim wherein said enclosures are adapted to permit removal or deposit of a portion of said compound, and to re-seal so as to maintain the contents of the enclosure intact.

9. Apparatus according to any preceding claim wherein at least a portion of the substrate is transparent.

10. A method of storing a plurality of chemical compounds for retrieval comprising the steps of:

i) disposing a chemical compound on a region of a substrate;

ii) retaining said chemical compound so that it is isolated from other compounds;

iii) arranging an address to be associated with said region; and

iv) repeating steps i) to iii) on different regions of said substrate.

11. A method according to claim 10 wherein one or more processing steps are performed on selected compounds on regions of the substrate.

12. A method according to claim 11 wherein the processing steps include chemical reactions with other chemicals or compounds so as to create products.

13. A method according to claim 11 or 12 wherein the products created are retained on the substrate or formed on or transferred on to a further substrate.

14. A method of retrieving a chemical compound from a plurality of stored compounds on a substrate from address information, comprising the steps of:

i) determining from said address information a position of the compound on the substrate; and

ii) displacing the substrate so that said region, supporting the compound, is presented for retrieval.

15. A method according to claim 1 wherein the term retrieval includes analysis, removal, examination and/or testing.

16. Apparatus substantially as herein described with reference to the figures.

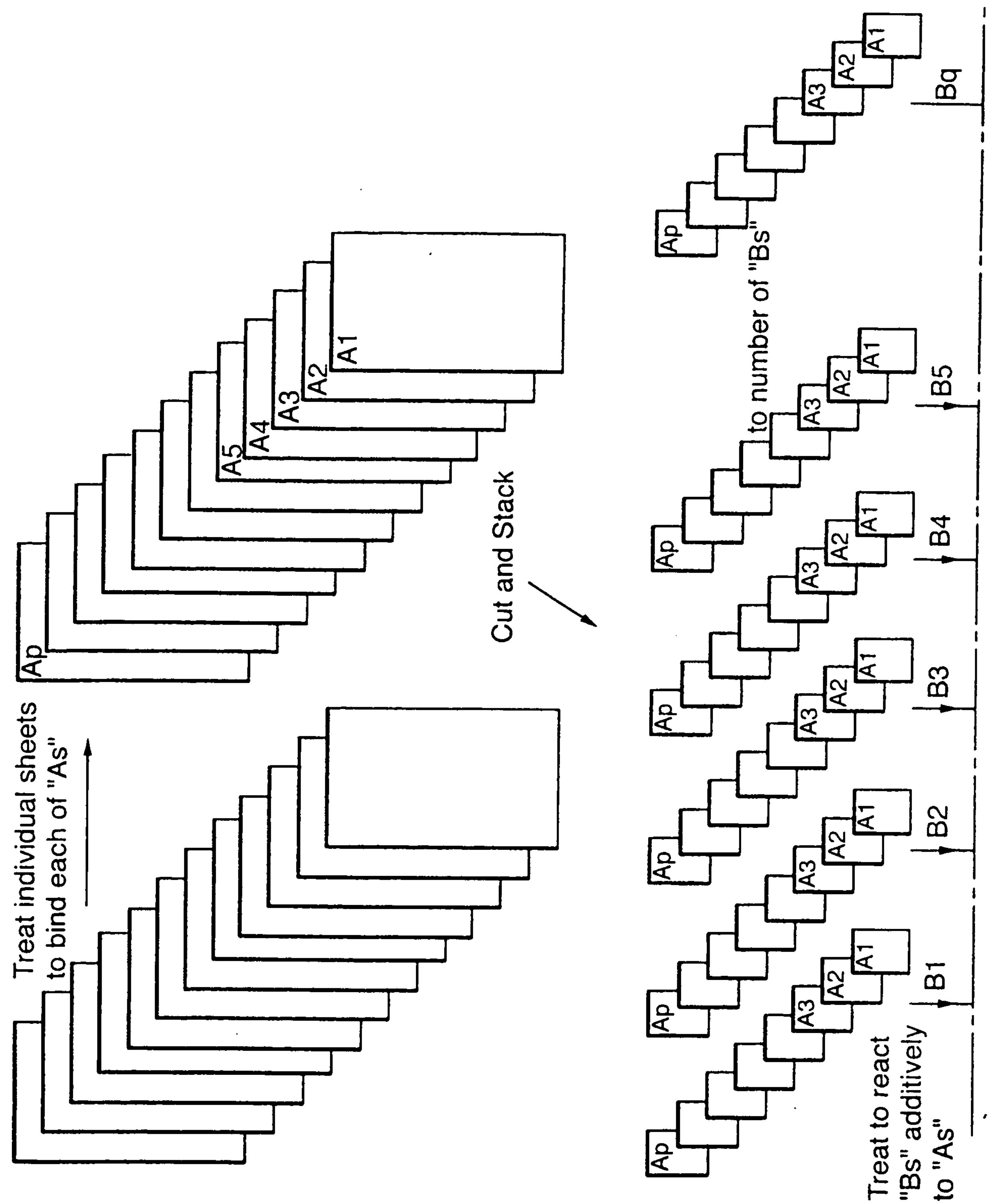

Treat individual sheets
to bind each of "As"
Ap
A5
A4
A3
A2
A1
Cut and Stack
Ap
A3
A2
A1
Bq
to number of "Bs"
B5
B4
B3
B2
B1
Treat to react
"Bs" additively
to "As"

Fig.1.

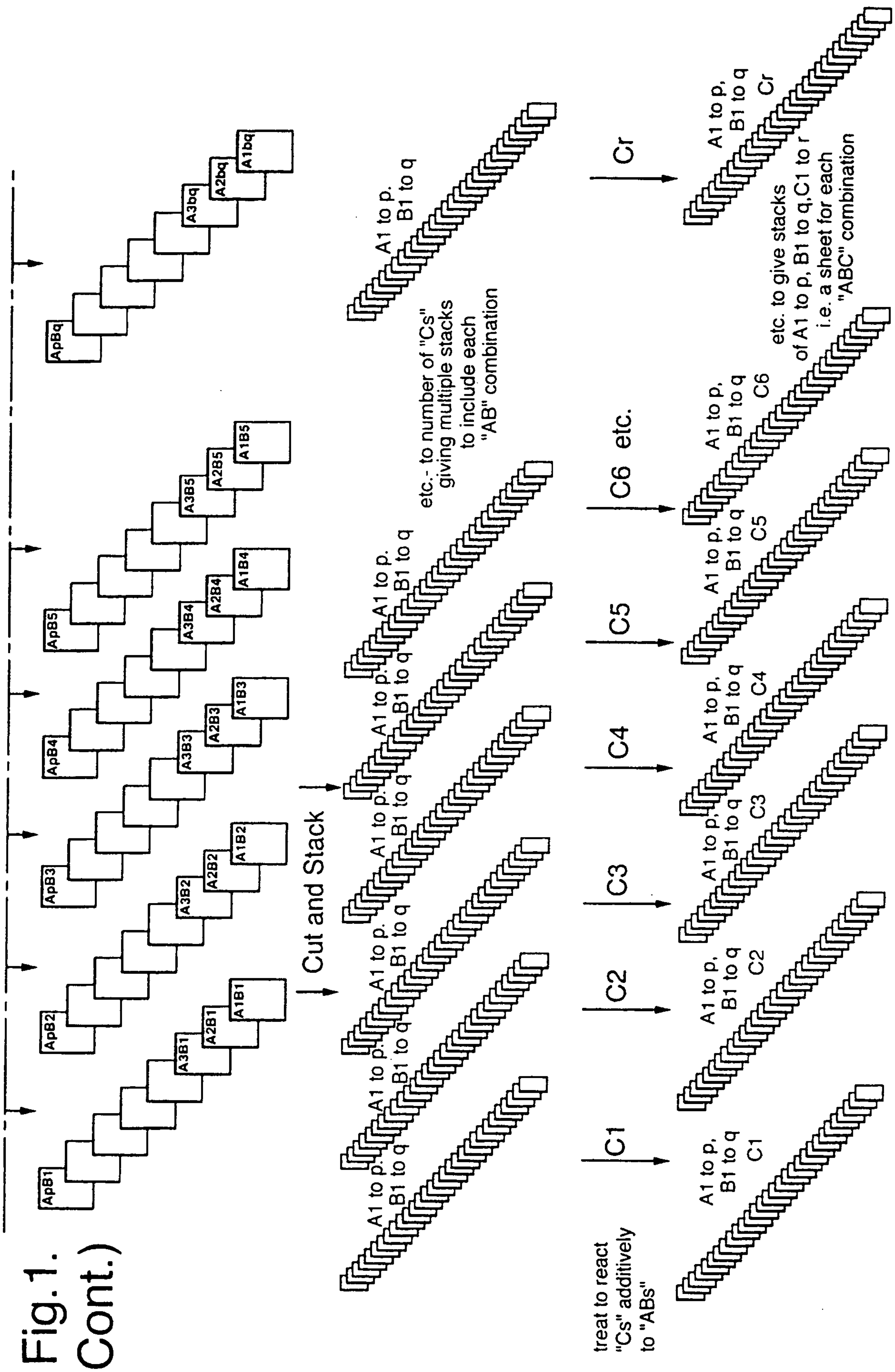
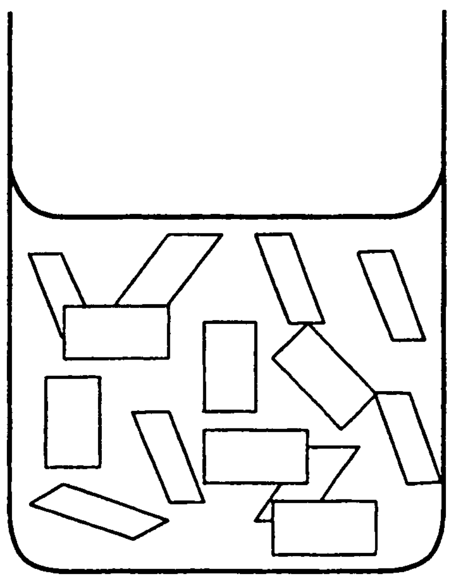

ApB1
A3B1
A2B1
A1B1
ApB2
A3B2
A2B2
A1B2
ApB3
A3B3
A2B3
A1B3
ApB4
A3B4
A2B4
A1B4
ApB5
A3B5
A2B5
A1B5
ApBq
A3bq
A2bq
A1bq
Cut and Stack
A1 to p.
B1 to q
etc.- to number of "Cs" giving multiple stacks to include each "AB" combination
treat to react "Cs" additively to "ABs"
C1
C2
C3
C4
C5
C6 etc.
Cr
A1 to p,
B1 to q
C1
C2
C3
C4
C5
C6
Cr
etc. to give stacks of A1 to p, B1 to q,C1 to r i.e. a sheet for each "ABC" combination

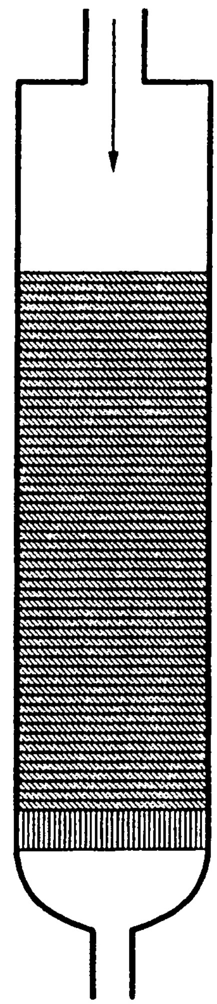
Fig.1. (Cont.)

Fig.2.



Processing planar substrates in free solution.

Generally need to read and re order after 2nd or later chemistry addition.



Processing planar substrates in filter stack arrangement.

?

Fig.3.

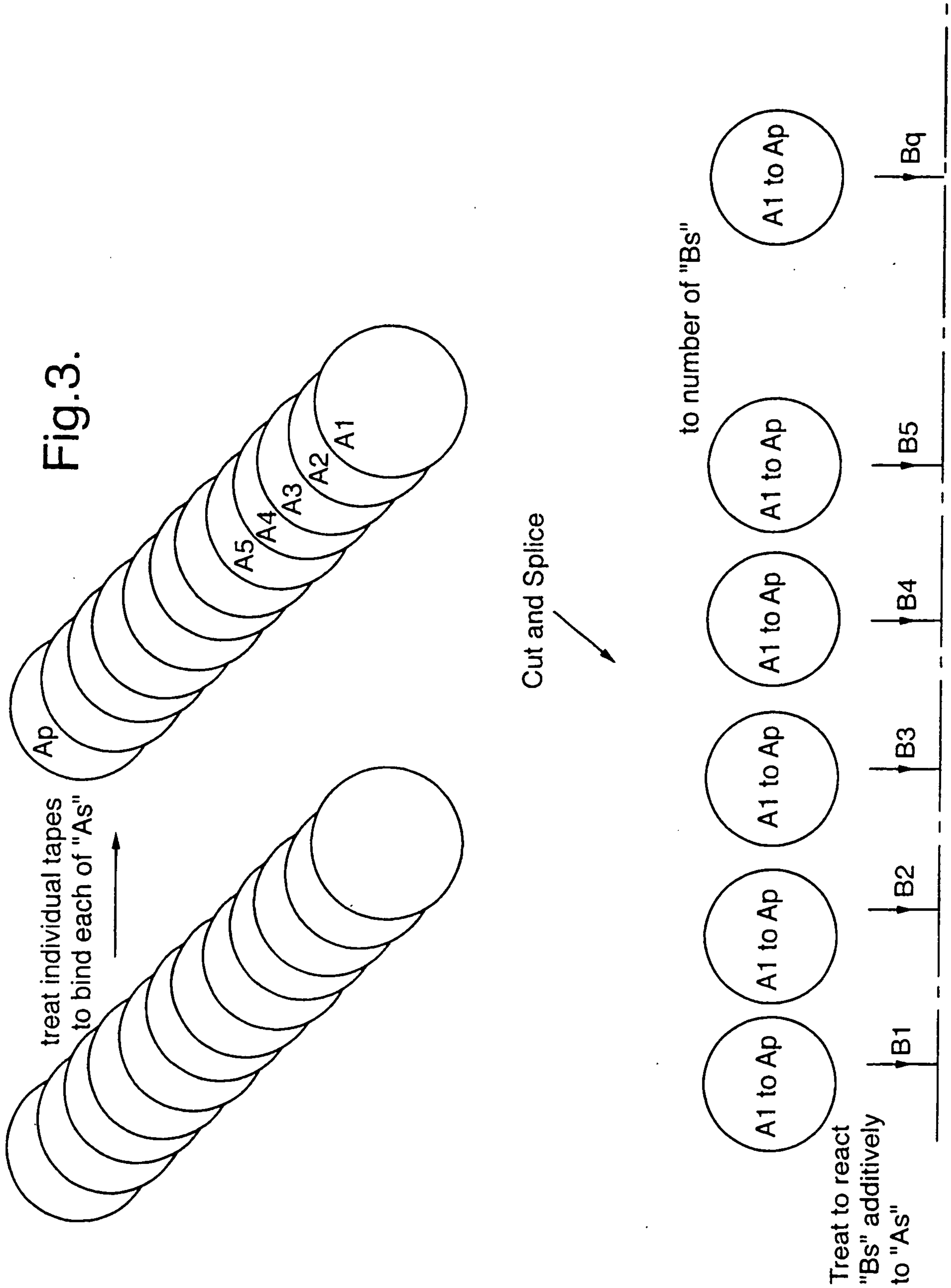

treat individual tapes
to bind each of "As"
Ap
A5
A4
A3
A2
A1
Cut and Splice
to number of "Bs"
A1 to Ap
A1 to Ap
A1 to Ap
A1 to Ap
A1 to Ap
A1 to Ap
B1
B2
B3
B4
B5
Bq
Treat to react
"Bs" additively
to "As"

Fig.3. (Cont.)

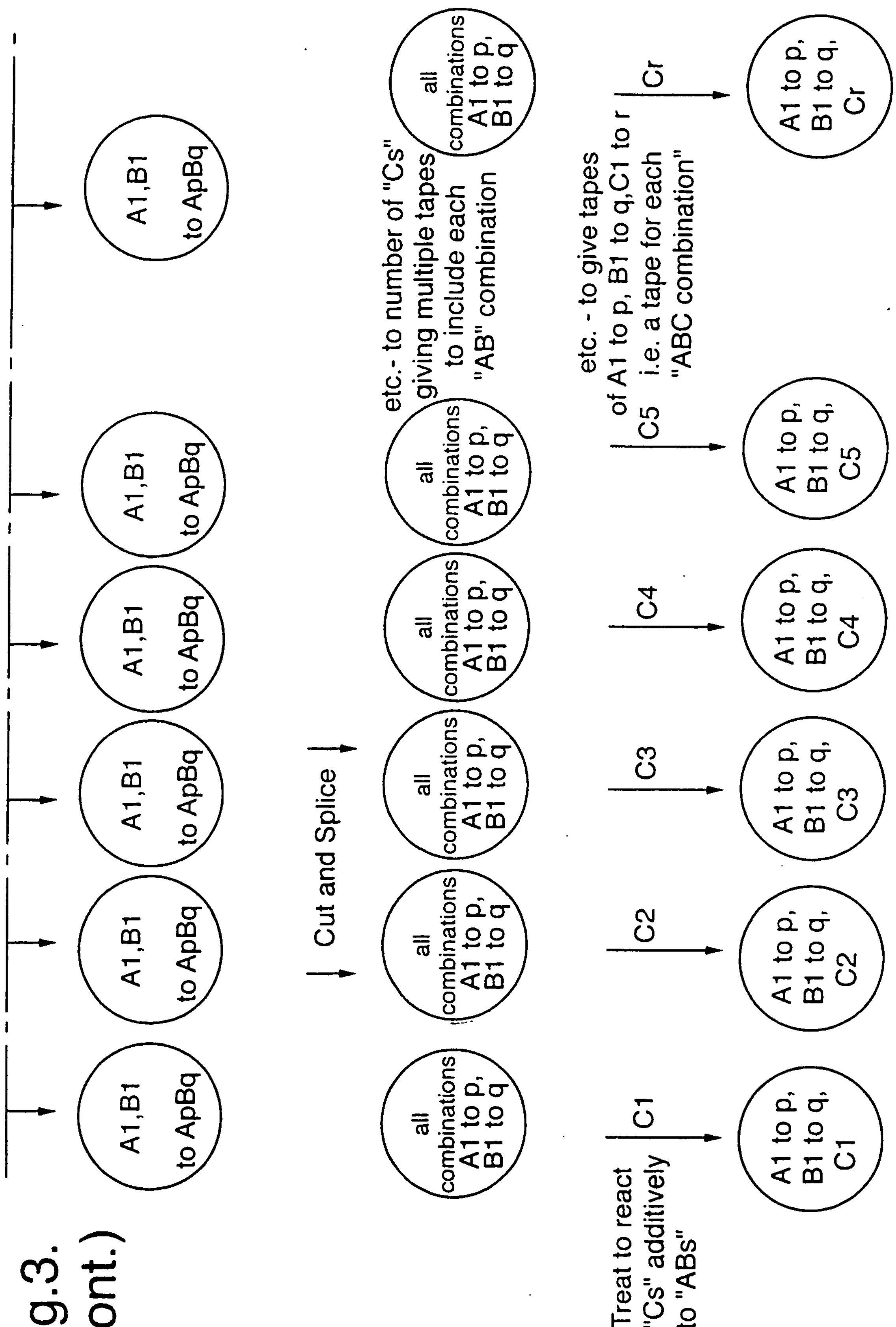

A1,B1 to ApBq
Cut and Splice
all combinations A1 to p, B1 to q
etc.- to number of "Cs" giving multiple tapes to include each "AB" combination
Treat to react "Cs" additively to "ABs"
C1
C2
C3
C4
C5
Cr
etc. - to give tapes of A1 to p, B1 to q,C1 to r i.e. a tape for each "ABC combination"
A1 to p, B1 to q, C1
A1 to p, B1 to q, C2
A1 to p, B1 to q, C3
A1 to p, B1 to q, C4
A1 to p, B1 to q, C5
A1 to p, B1 to q, Cr

Fig.4a.

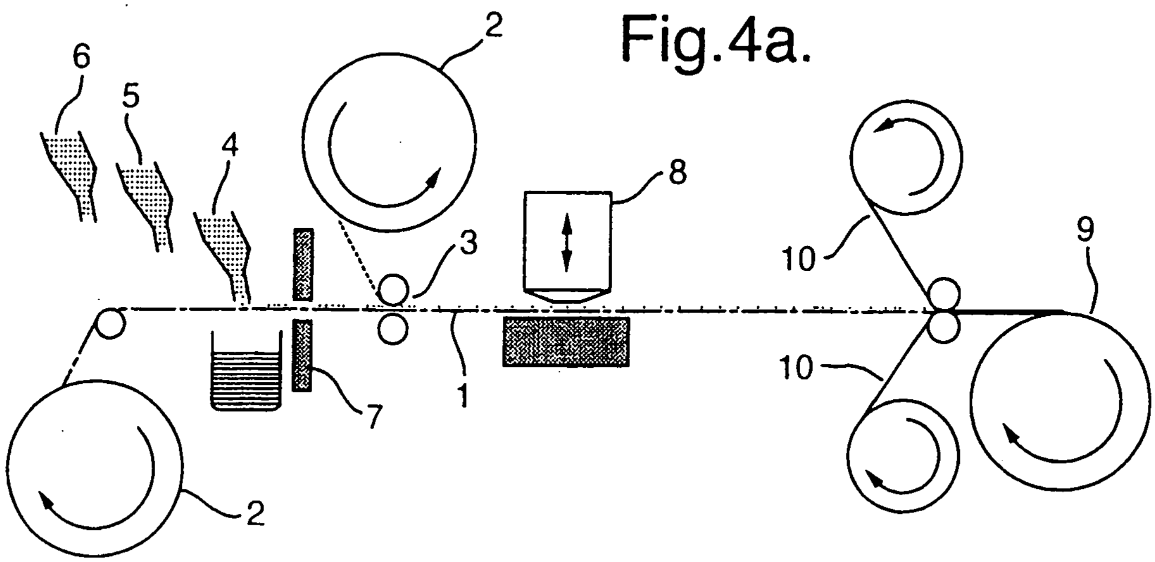



Fig.4b.

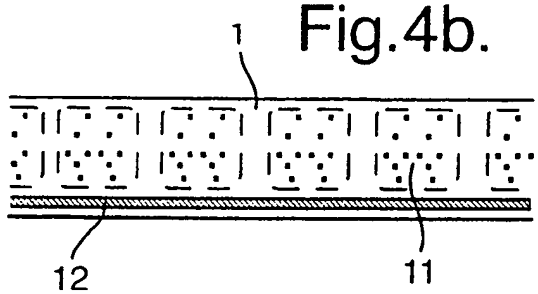



Fig.5.

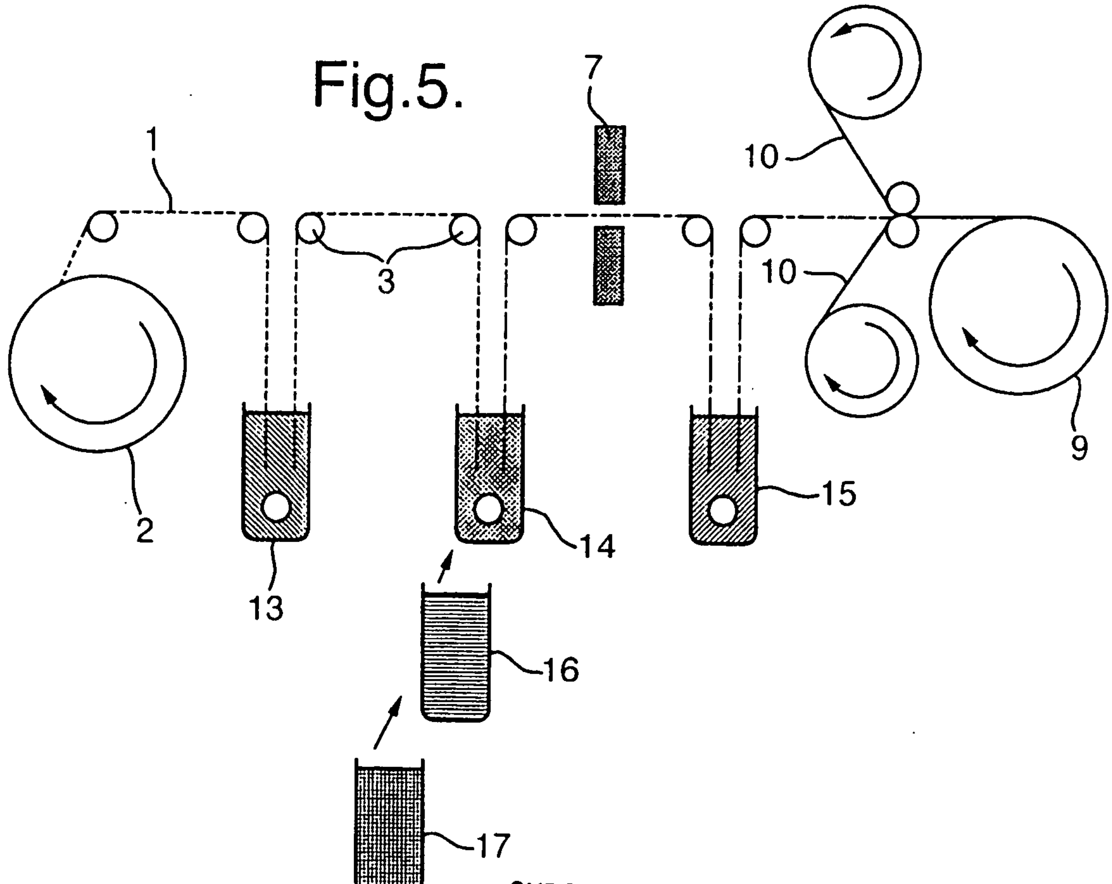


Fig.6.

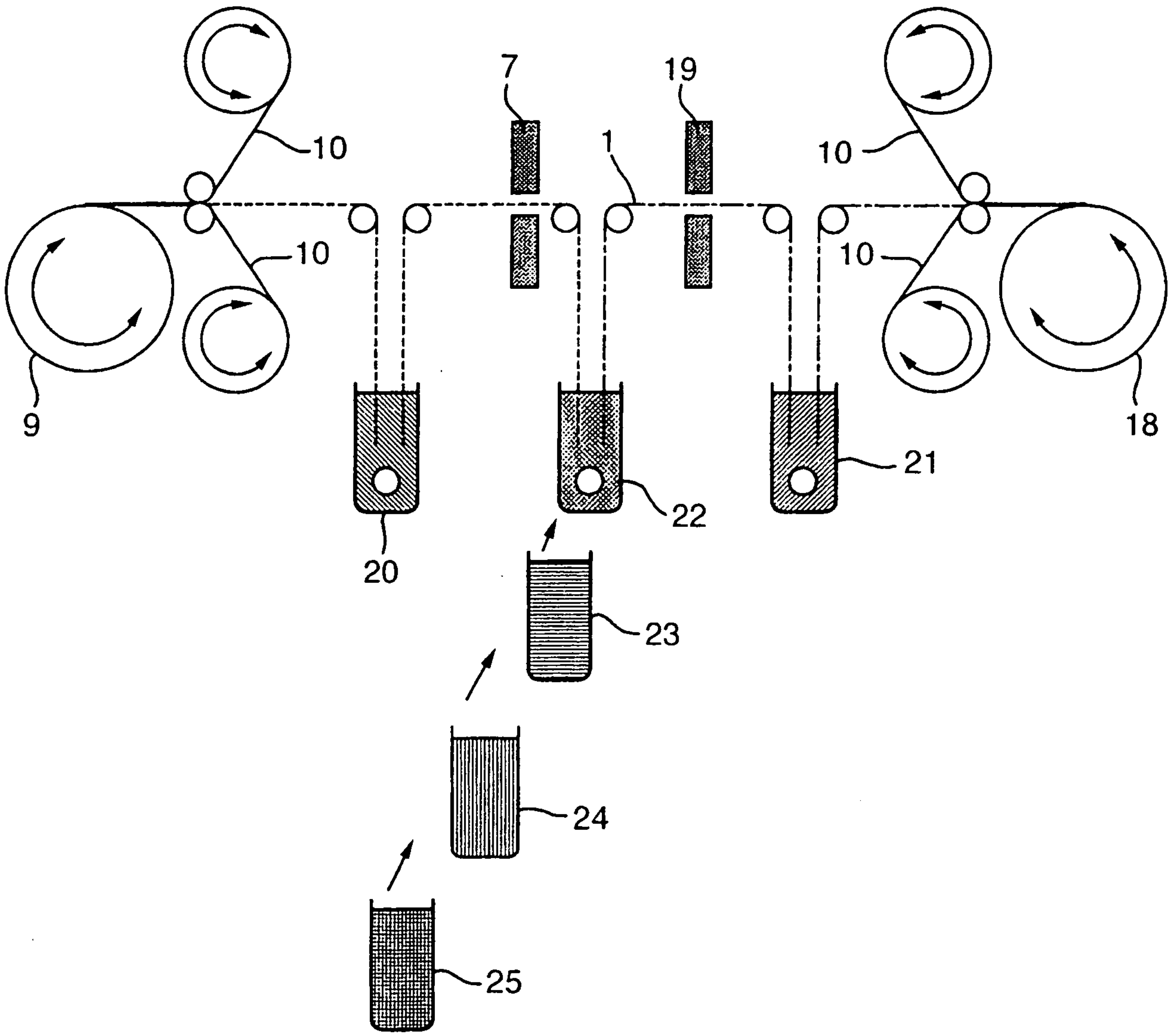


Fig.7.

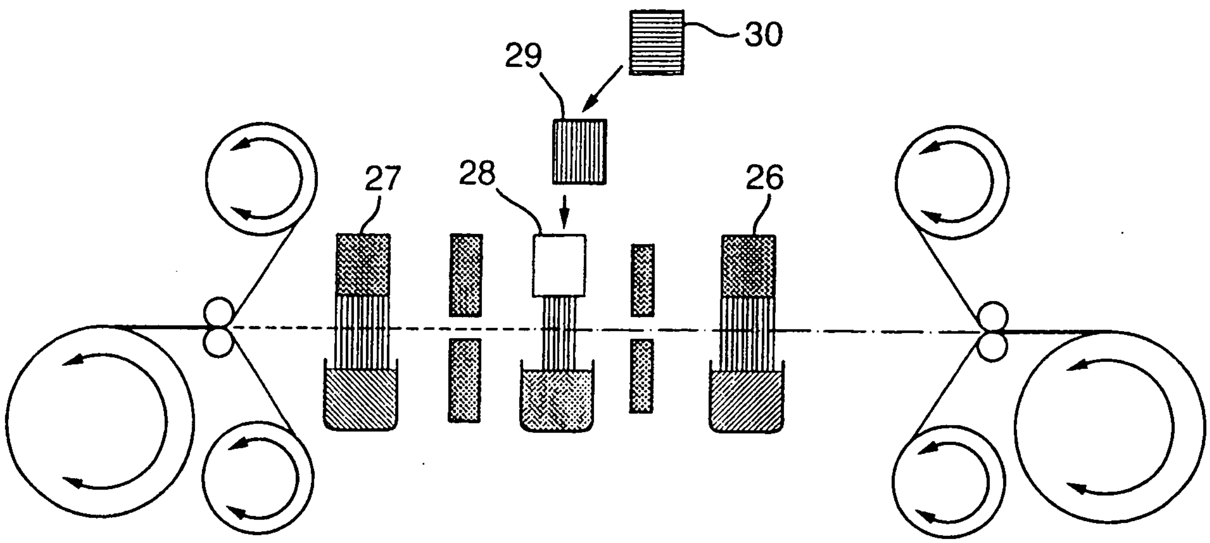



Fig.8.

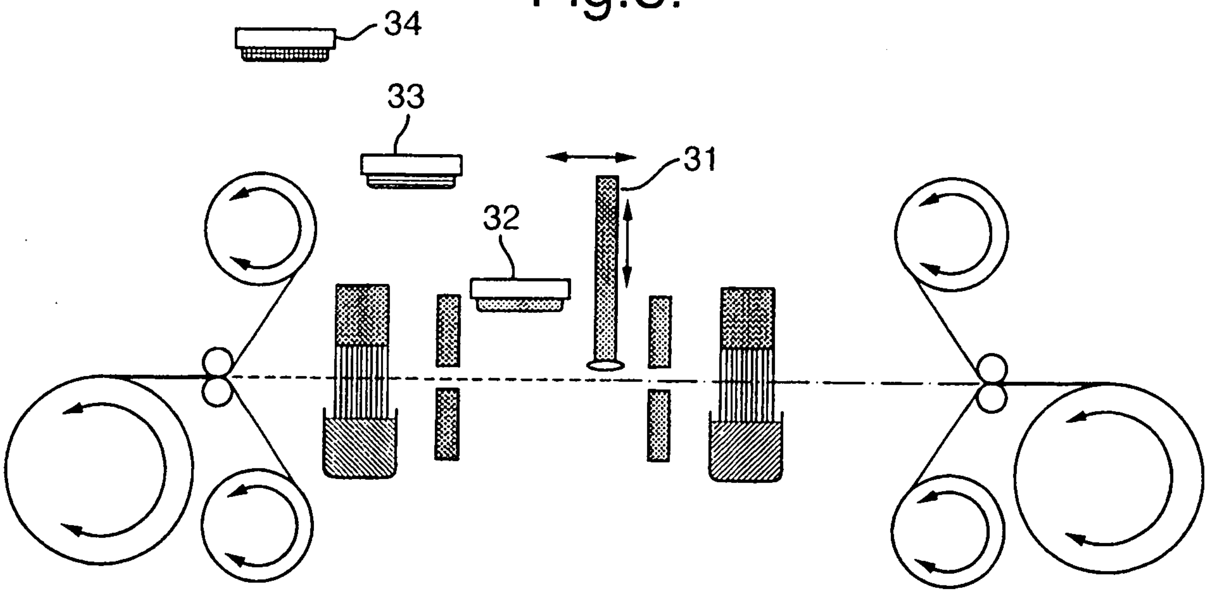


Fig.9.

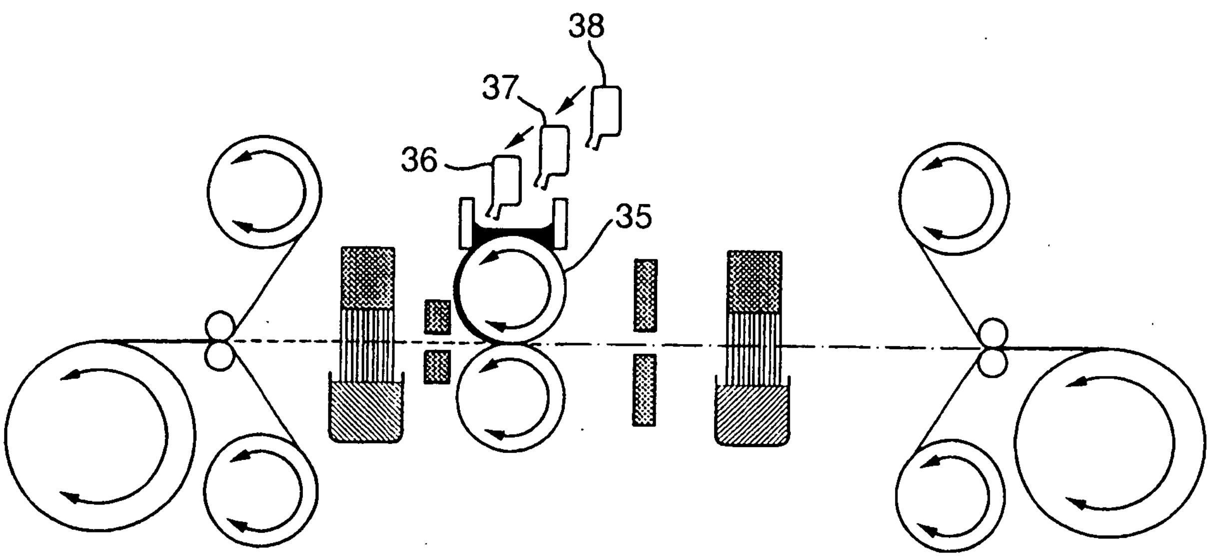



Fig.10.

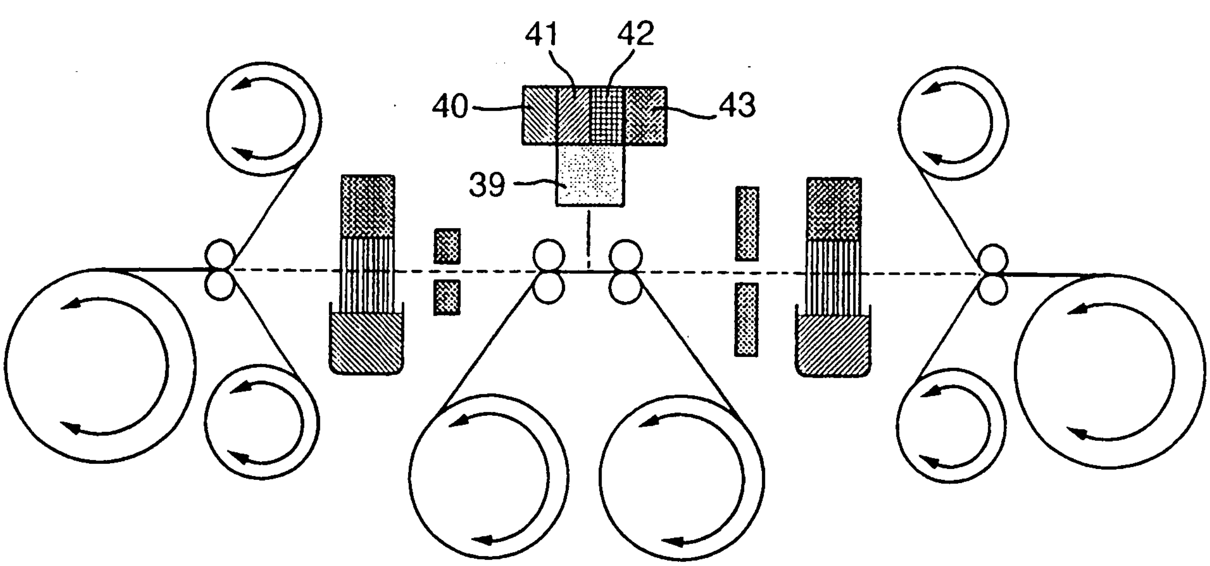


Fig.11.

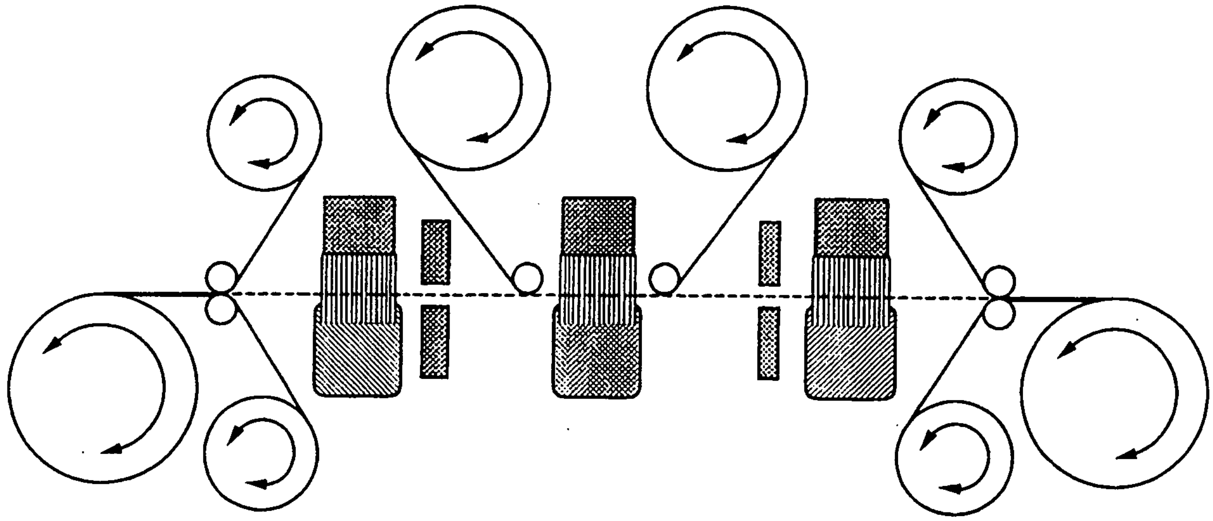


Fig.12.

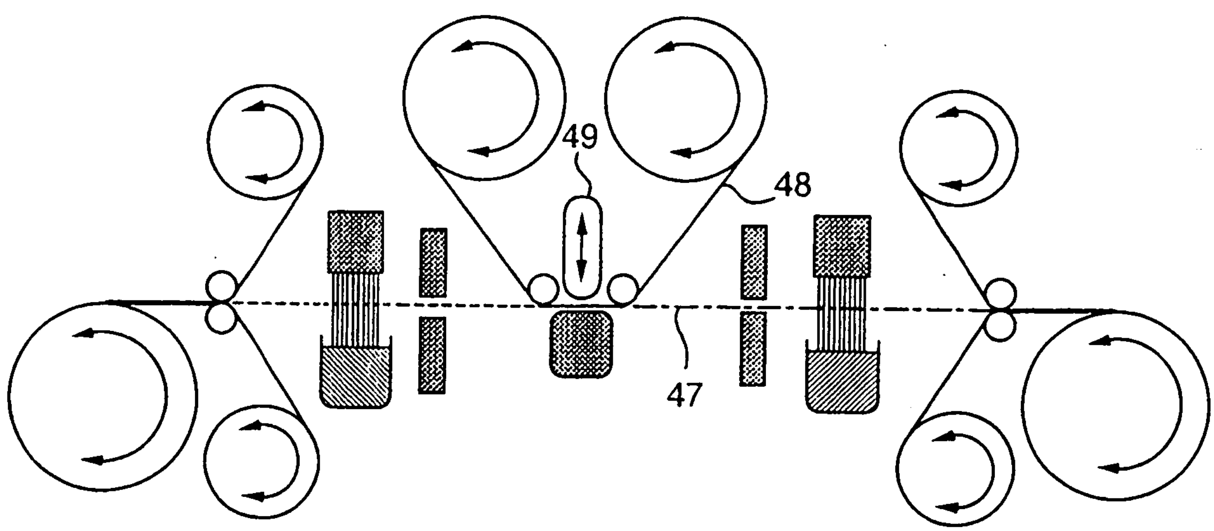


Fig.13a.

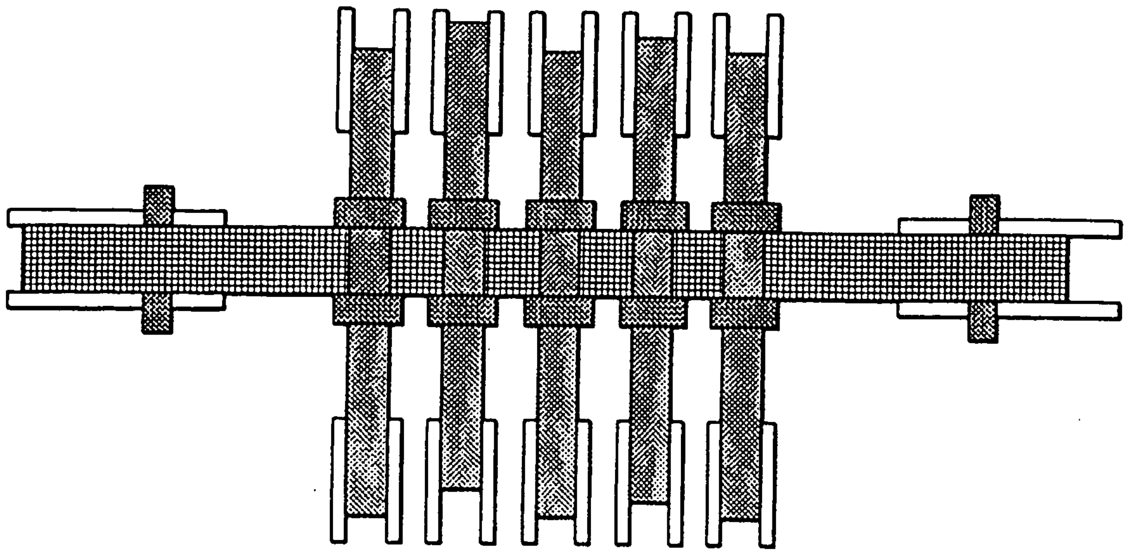


Fig.13b.

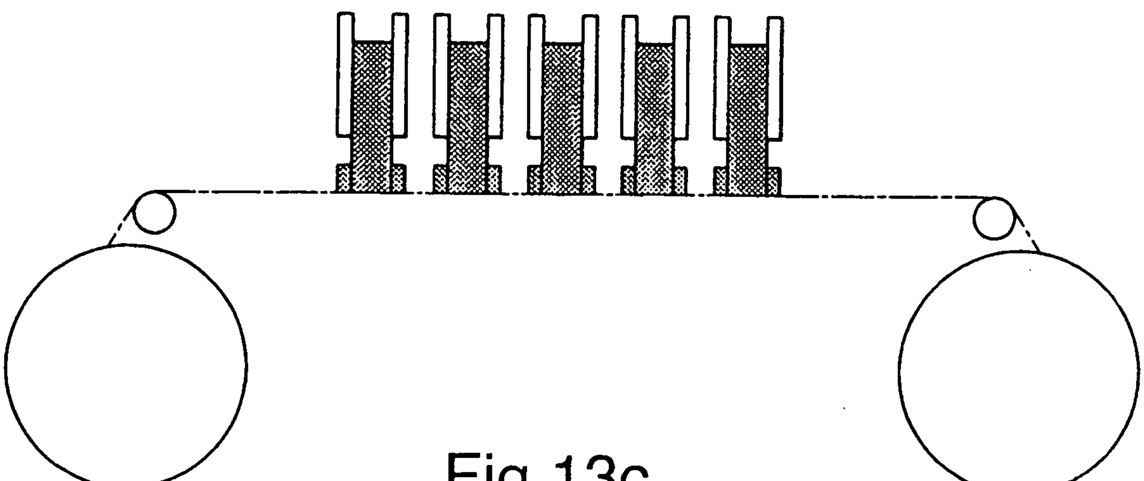


Fig.13c.